ARS RESEARCH, GRAPES AND HUMAN NUTRITION

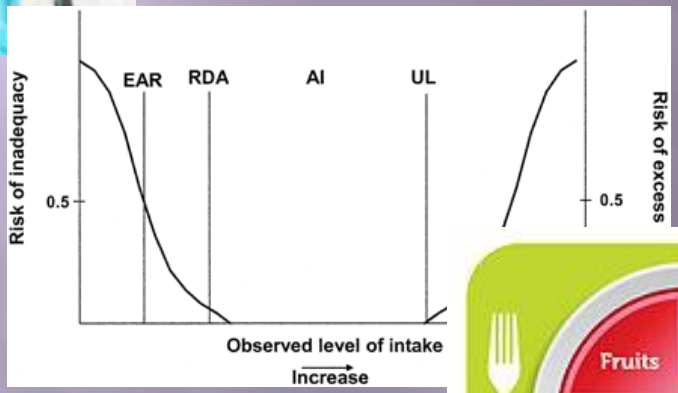
John W. Finley *
USDA-ARS

* Views expressed herein are those of J. Finley and do not necessarily represent those of the USDA or any other government agency

USDA-ARS PROGRAM IN HUMAN NUTRITION:

Spanning the Divide from Basic Research to Healthy Outcomes

Basic Research



Dietary Requirements

Dietary Guidelines

Healthy People

Research Capability

Grand Forks HNRC; Emphasis on Obesity

Tuft's HNRC; Emphasis on Aging

Western HNRC; Emphasis on Basic Research; Whole foods

Arkansas HNRC; Emphasis on Children

Beltsville HNRC; Emphasis on Basic Research; Whole foods

Baylor HNRC; Emphasis on Children

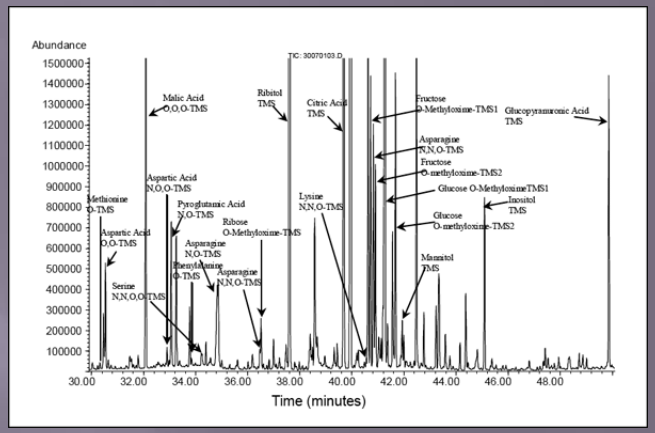
Washington
Montana
North Dakota
Minnesota
Idaho
South Dakota
Wisconsin
Michigan
Wyoming
Nebraska
Iowa
Nevada
Illinois
Indiana
Ohio
Pennsylvania
California
Utah
Colorado
Missouri
West
Kentuck
Arizona
New Mexico
Tennessee
Arkansas
Mississippi
Alabama
Georgia
Texas
Louisiana
Florida
Maine
Vermont
New York
New Hampshire
Massachusetts
Connecticut
Rhode Island
New Jersey
Delaware
Maryland

Total budget: $85 m
~ 200 scientists

Basic Research

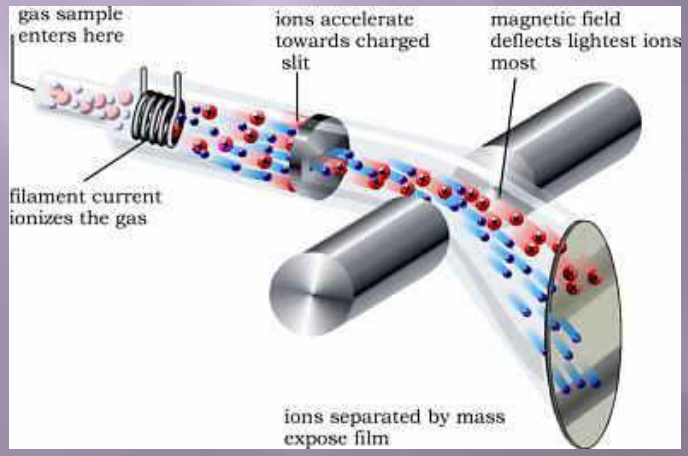
Diet and Genetics

Ordovás JM, Robertson R, Cléirigh EN. **Gene-gene and gene-environment interactions defining lipid-related traits.** Curr Opin Lipidol. 2011 Apr;22(2):129-36. Review.



Metabolomics

Psychogios N, Hau DD, Peng J, Guo AC, Mandal R, Bouatra S, Sinelnikov I, Krishnamurthy R, Eisner R, Gautam B, Young N, Xia J, Knox C, Dong E, Huang P, Hollander Z, Pedersen TL, Smith SR, Bamforth F, Greiner R, McManus B, Newman JW, Goodfriend T, Wishart DS. **The human serum metabolome**. PLoS One. 2011 Feb 16;6(2):e16957.



Analytical Methodology

Byrdwell WC. **"Dilute-and-shoot" triple parallel mass spectrometry method for analysis of vitamin D and triacylglycerols in dietary supplements.** Anal Bioanal Chem. 2011 Dec;401(10):3317-34

Research Supporting Nutrient Requirements

The American Journal of
CLINICAL NUTRITION
The American Journal of Clinical Nutrition
American Journal of Clinical Nutrition, Vol. 88, No. 2, 356–363, August 2008

Vitamin K, circulating cytokines, and bone mineral density in older men and women

M Kyla Shea, Gerard E Dallal, Bess Dawson-Hughes, José M Ordovas, Christopher J O'Donnell, Caren M Gundberg, James W Peterson and Sarah Booth

Osteoporos Int (2010) 21:1151–1154
DOI 10.1007/s00198-010-1285-3

POSITION PAPER

IOF position statement: vitamin D recommendations for older adults

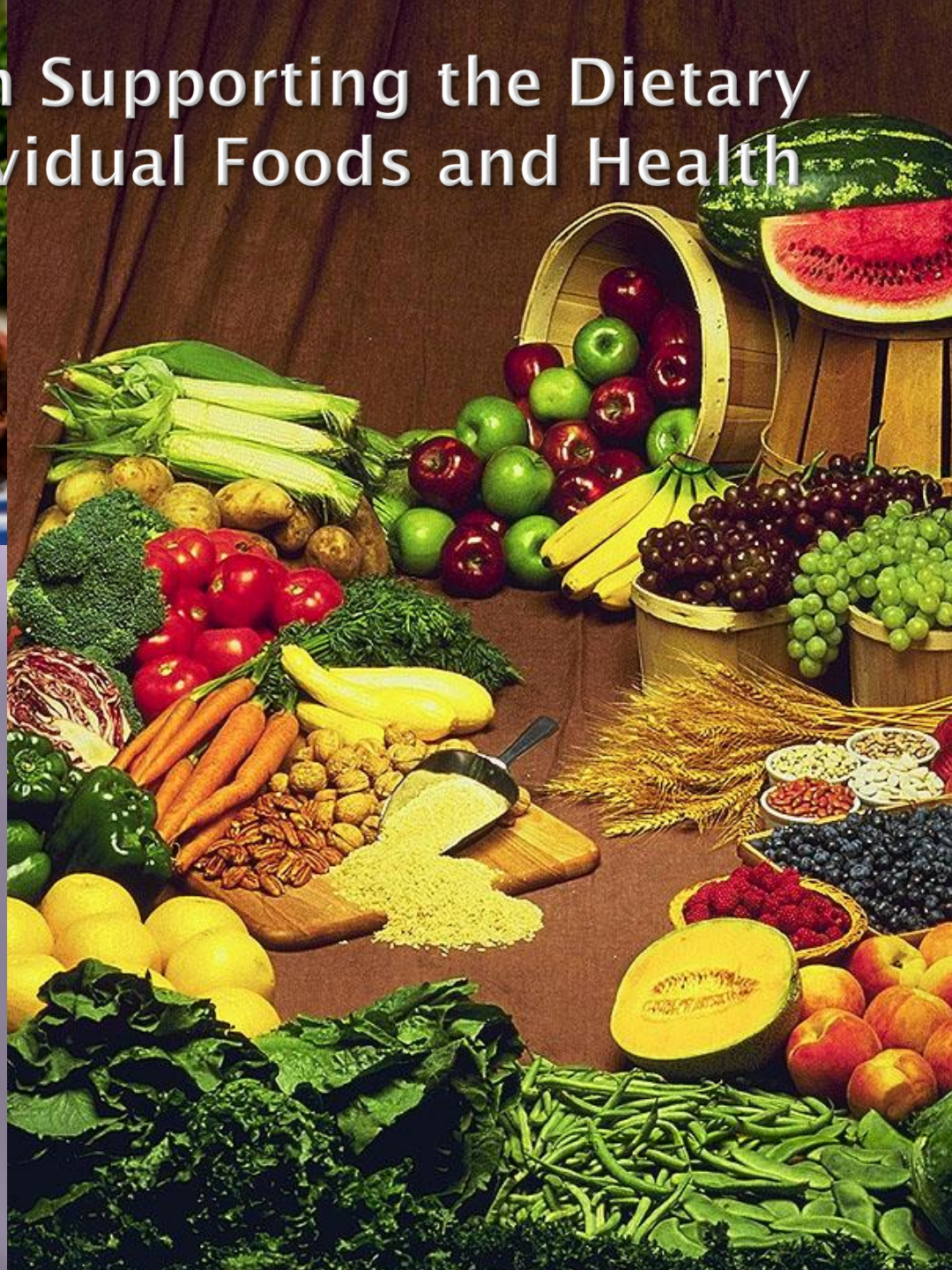
B. Dawson-Hughes · J.-P. Bonjour · S. Boonen · P. Burckhardt · G. E.-H. Fuleihan · R. G. Josse · P. Lips · J. Morales-Torres · N. Yoshimura

The American Journal of
CLINICAL NUTRITION
The American Journal of Clinical Nutrition
American Journal of Clinical Nutrition, Vol. 86, No. 4, 1054–1063, October 2007

Calcium requirements: new estimations for men and women by cross-sectional statistical analyses of calcium balance data from metabolic studies

Curtiss Hunt & LuAnn K Johnson
From the US Department of Agriculture, Agricultural Research Service, Grand Forks Human Nutrition Research Center, Grand Forks, ND

Applied Research Supporting the Dietary Guidelines: Individual Foods and Health



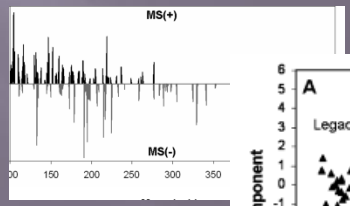
- Consumption of WHOLE FOODS not nutrients
  - Variability of foods
  - Dietary interactions
- The preeminence of DIET over Individual Foods

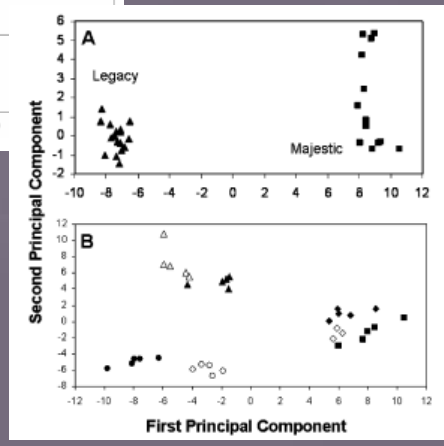
USDA-ARS: Integrating Human Nutrition with the Food Supply

APPLIED RESEARCH SUPPORTING THE DIETARY GUIDELINES: INDIVIDUAL FOODS AND HEALTH

Charron CS, Kurilich AC, Clevidence BA, Simon PW, Harrison DJ, Britz SJ, Baer DJ, Novotny JA. **Bioavailability of anthocyanins from purple carrot juice: effects of acylation and plant matrix.** J Agric Food Chem. 2009 Feb 25;57(4):1226-30.

Raatz SK, Golovko MY, Brose SA, Rosenberger TA, Burr GS, Wolters WR, Picklo MJ Sr. **Baking reduces prostaglandin, resolvin, and hydroxy-fatty acid content of farm-raised Atlantic salmon (Salmo salar).** J Agric Food Chem. 2011 Oct 26;59(20):11278-86





Luthria DL, Lin LZ, Robbins RJ, Finley JW, Banuelos GS, Harnly JM. **Discriminating between cultivars and treatments of broccoli using mass spectral fingerprinting and analysis of variance-principal component analysis.** J Agric Food Chem. 2008 Nov 12;56(21):9819-27.

APPLIED RESEARCH SUPPORTING THE DIETARY GUIDELINES: INDIVIDUAL FOODS AND HEALTH

Am J Clin Nutr. 2009 Jun;89(6):1776-83. Epub 2009 Apr 15. **Golden Rice is an effective source of vitamin A.** Tang G, Qin J, Dolnikowski GG, Russell RM, Grusak MA.

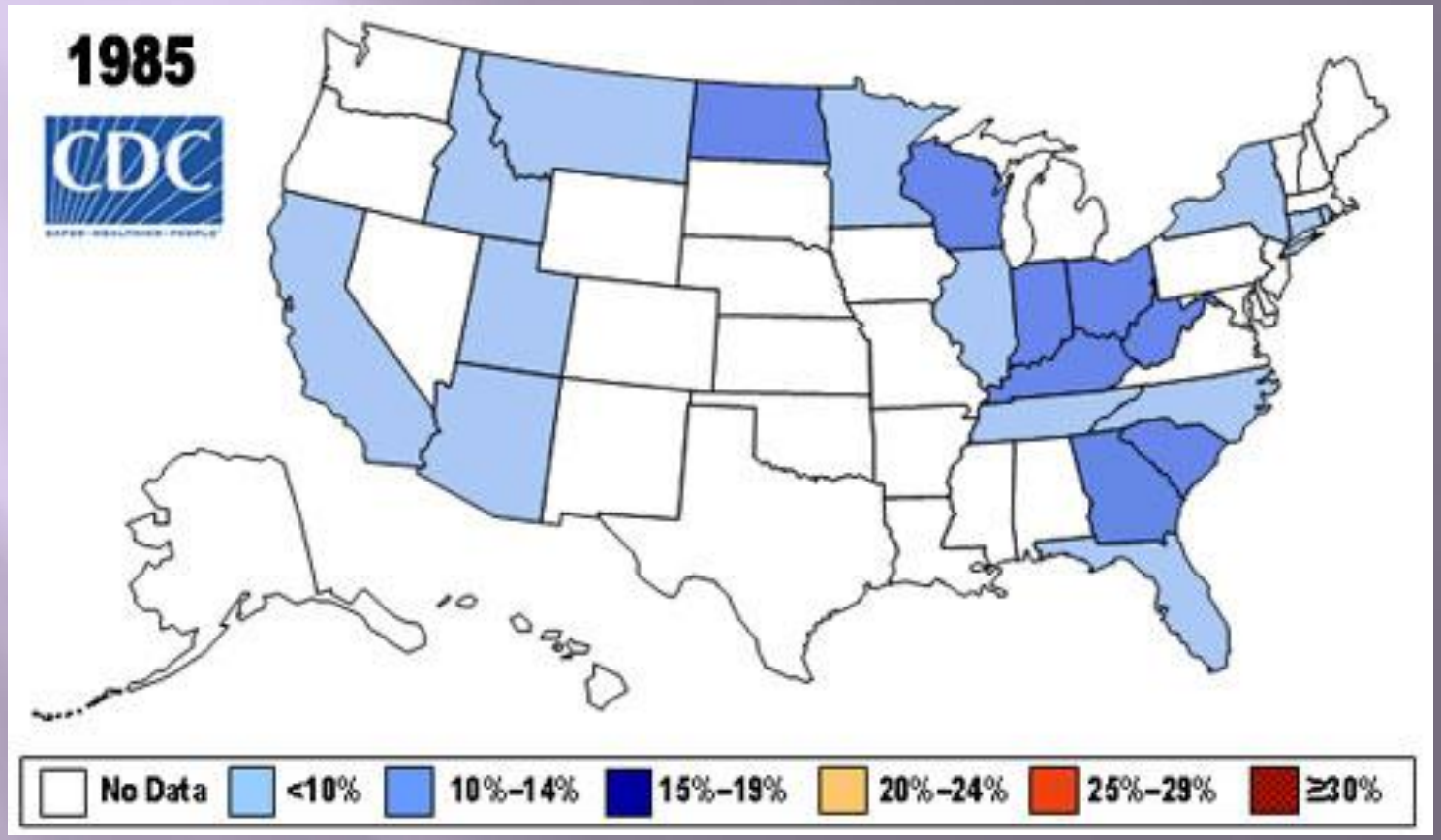
Research outside of the Human Nutrition Program

Lee J, Finn CE.

Anthocyanins and other polyphenolics in American elderberry (Sambucus canadensis) and European elderberry (S. nigra) cultivars. J Sci Food Agric. 2007 Nov;87(14):2665-75.

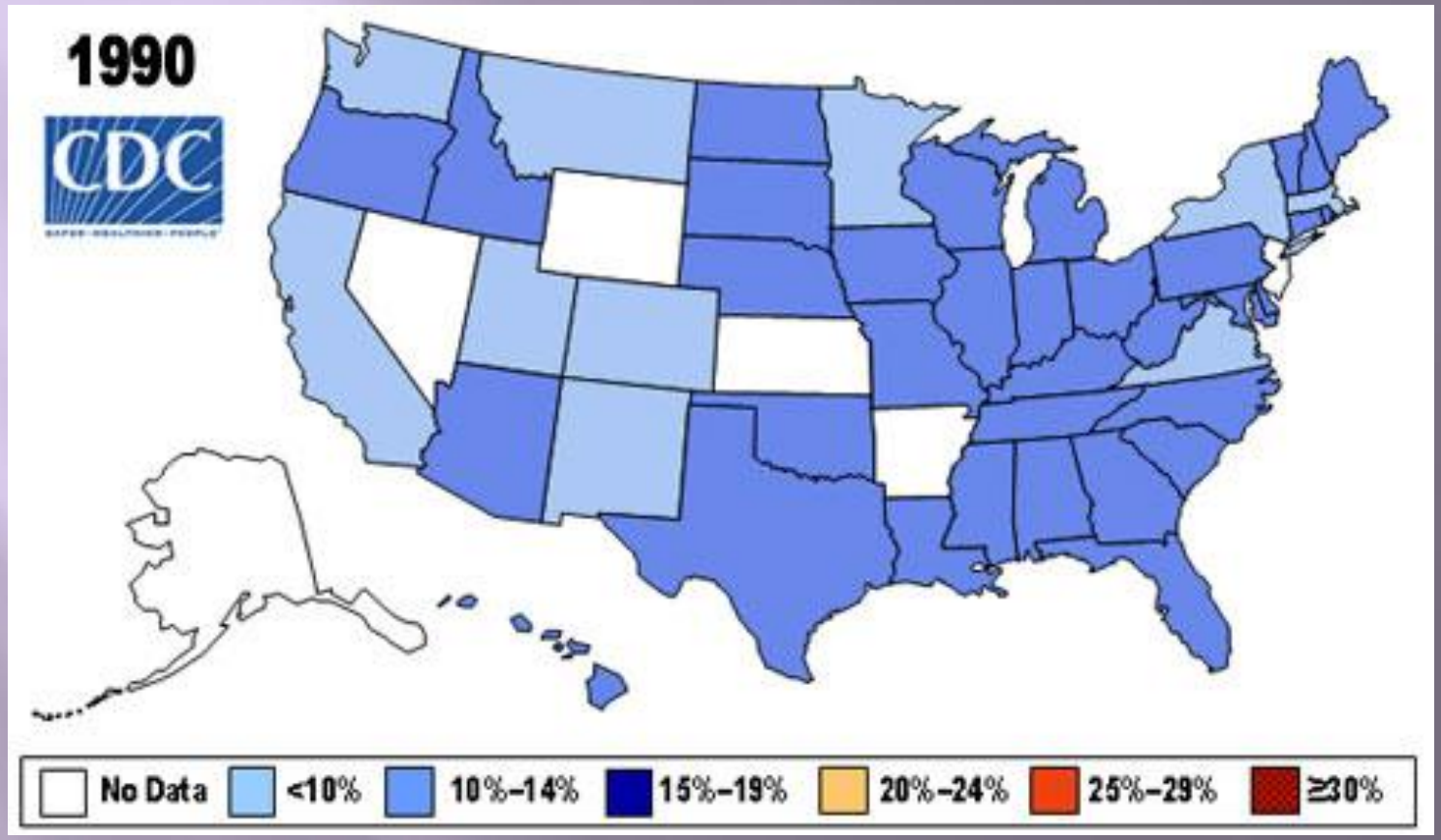
Percent of Obese (BMI ≥ 30) in U.S. Adults

APPLIED RESEARCH DIRECTED TOWARD DEVELOPING HEALTHIER PEOPLE



- **Obesity – A National Epidemic**
- **A major focus of USDA-ARS**

Percent of Obese (BMI ≥ 30) in U.S. Adults



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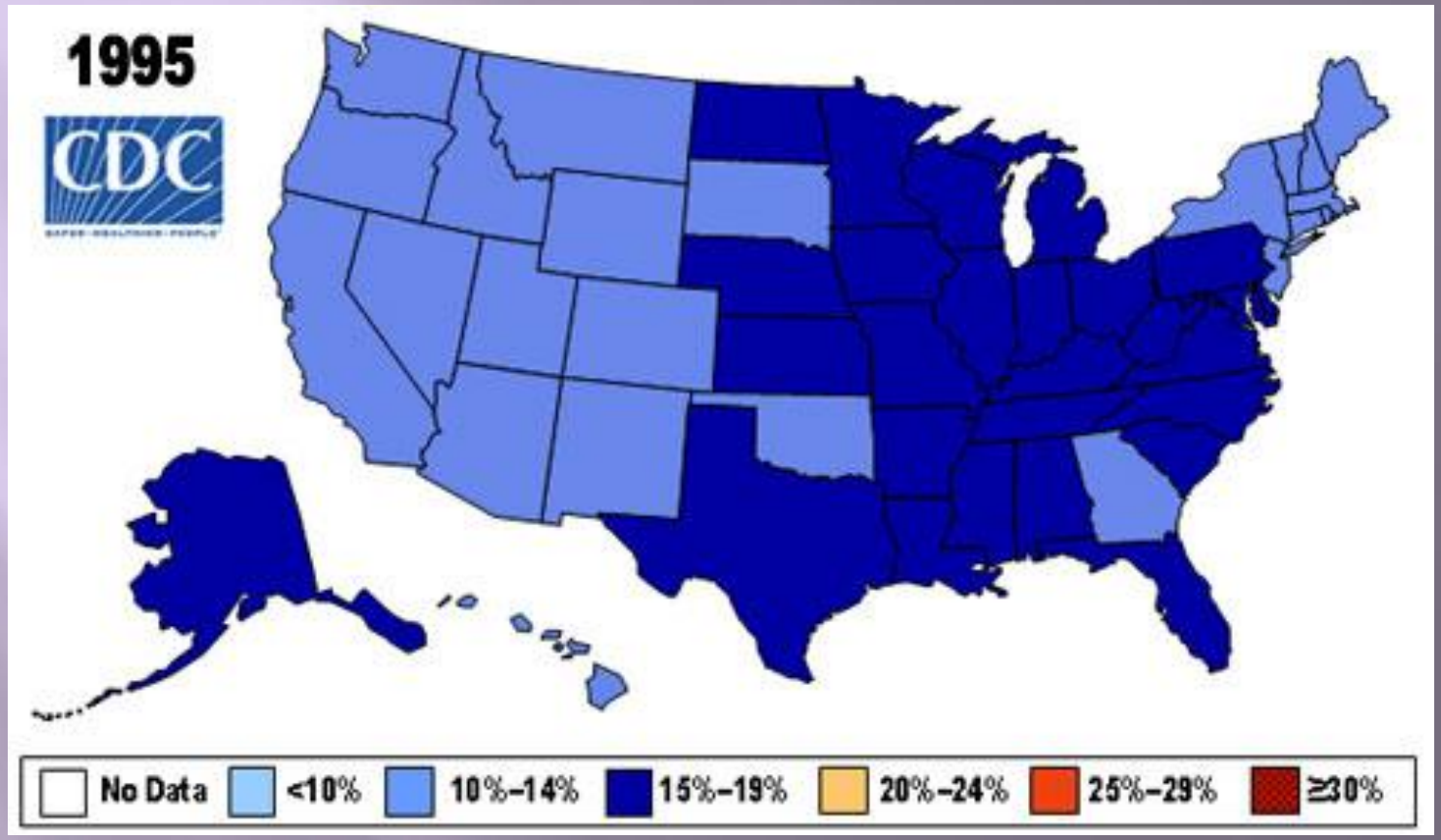

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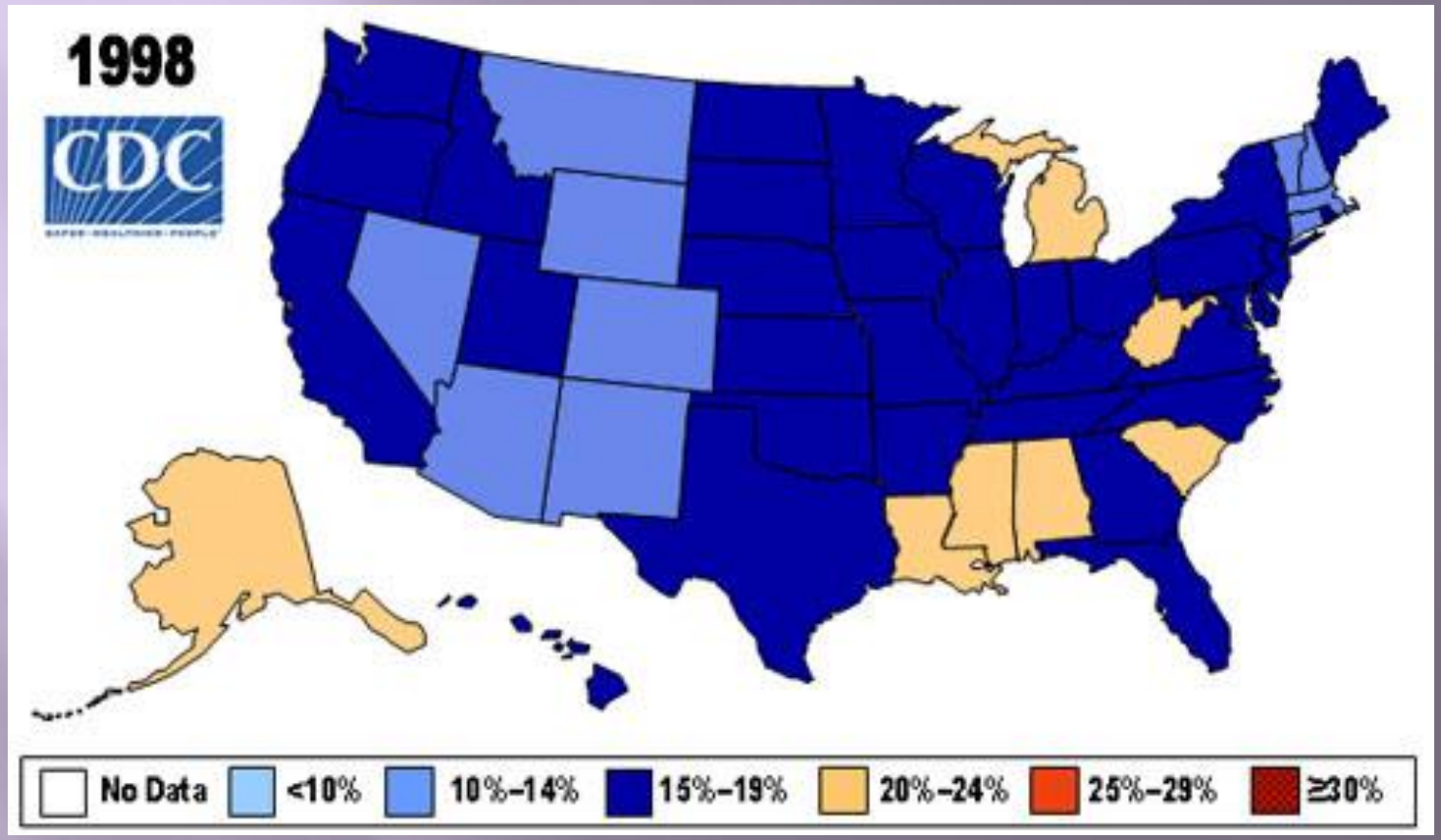

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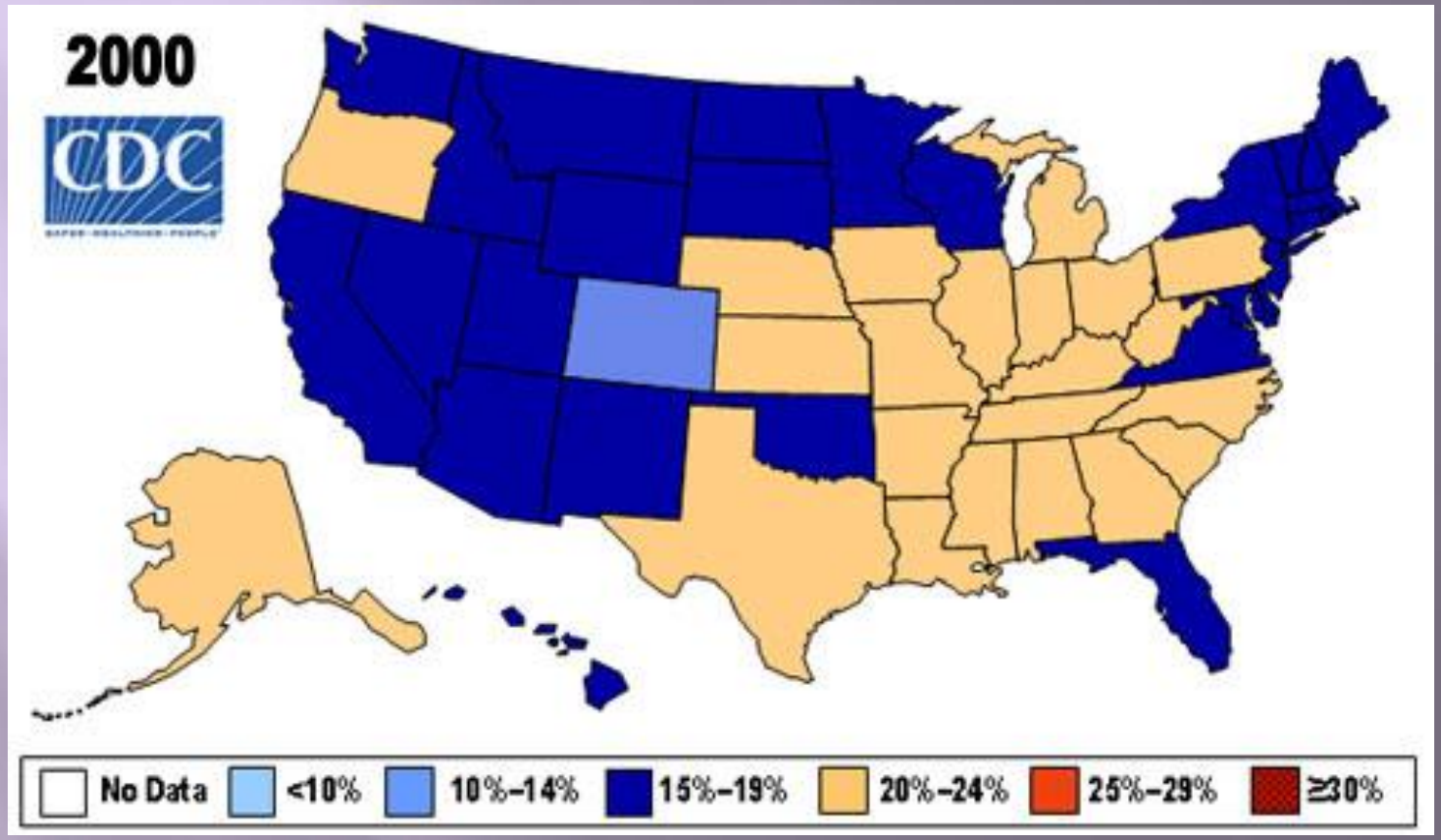

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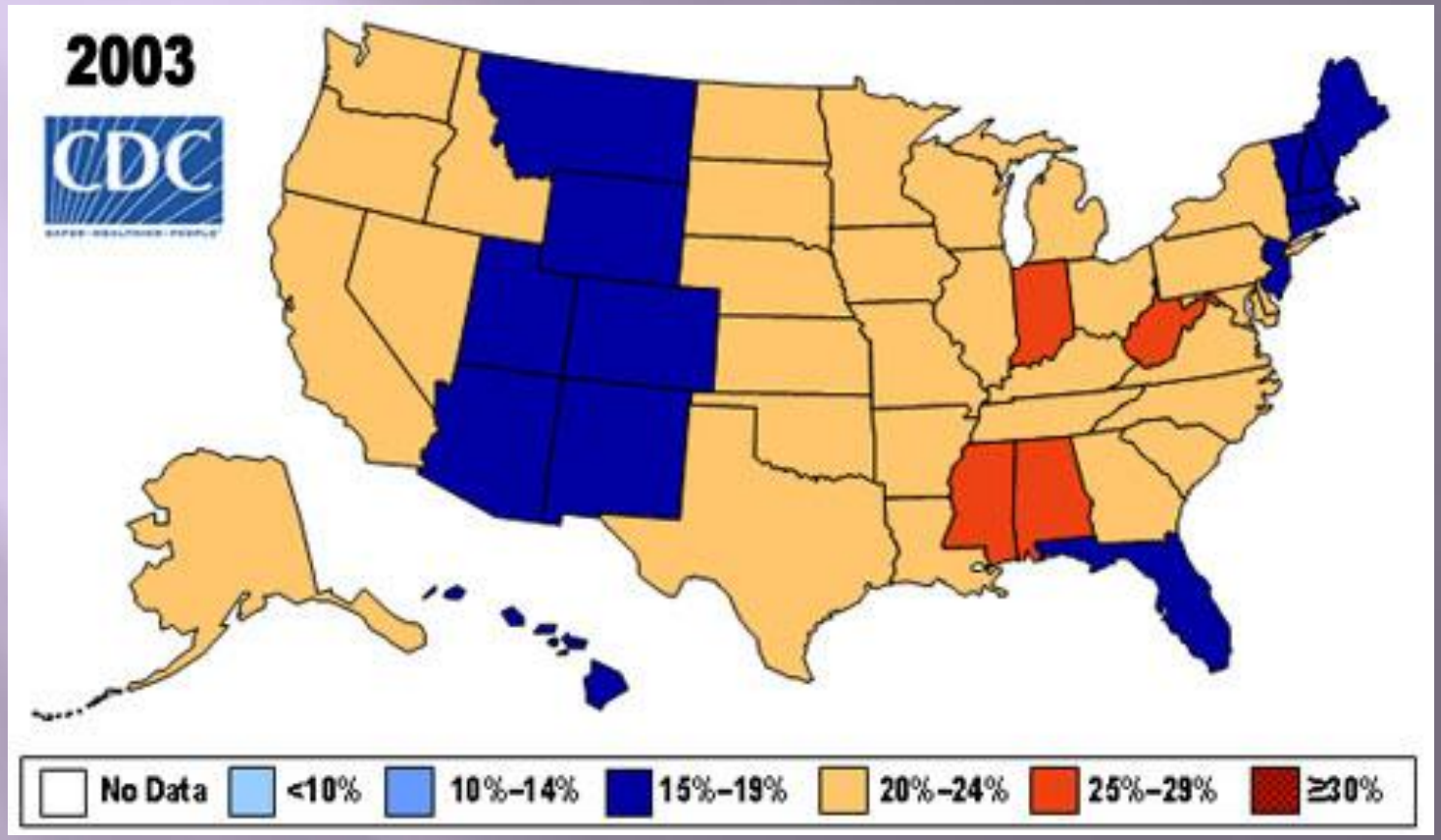

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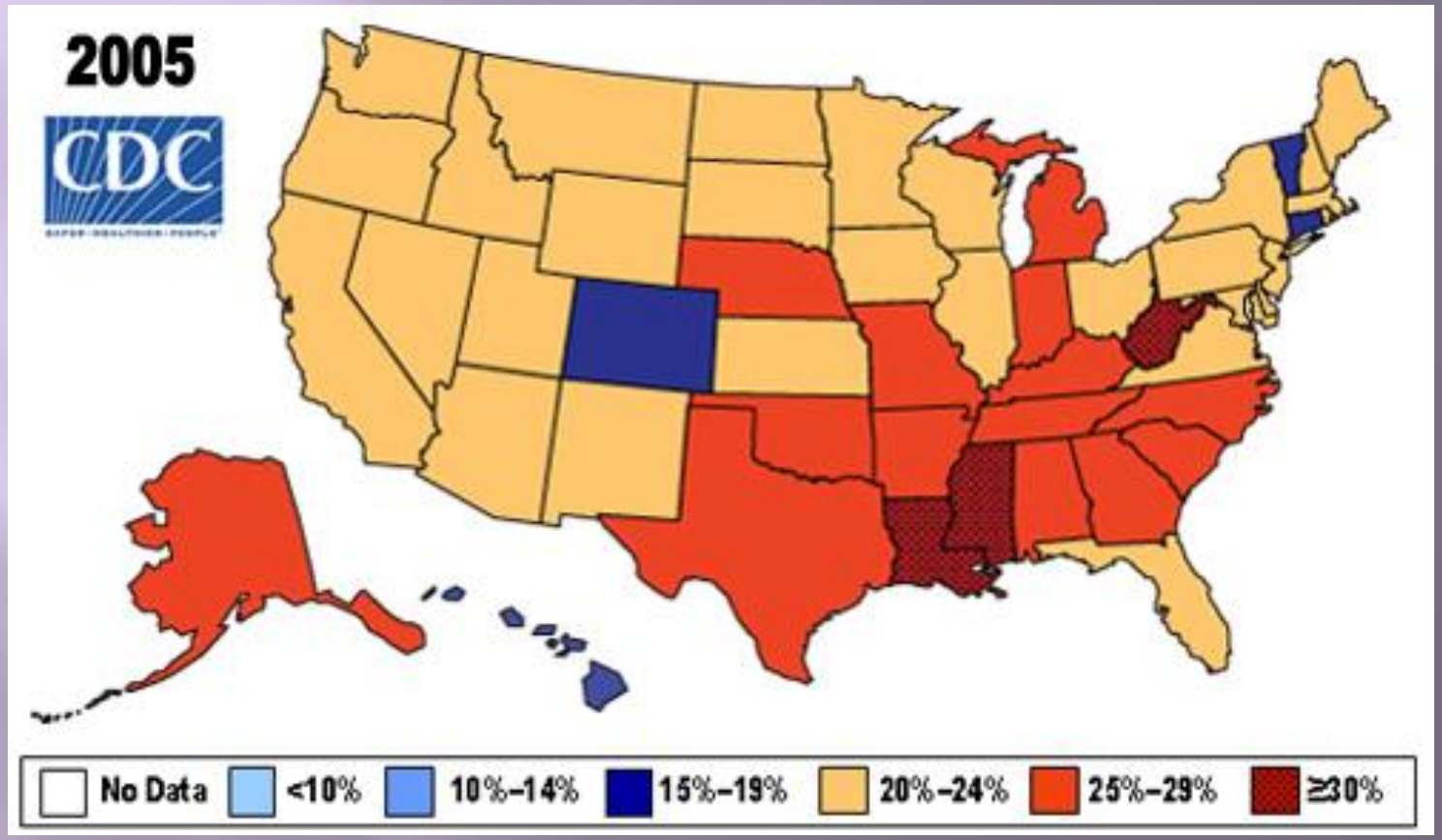
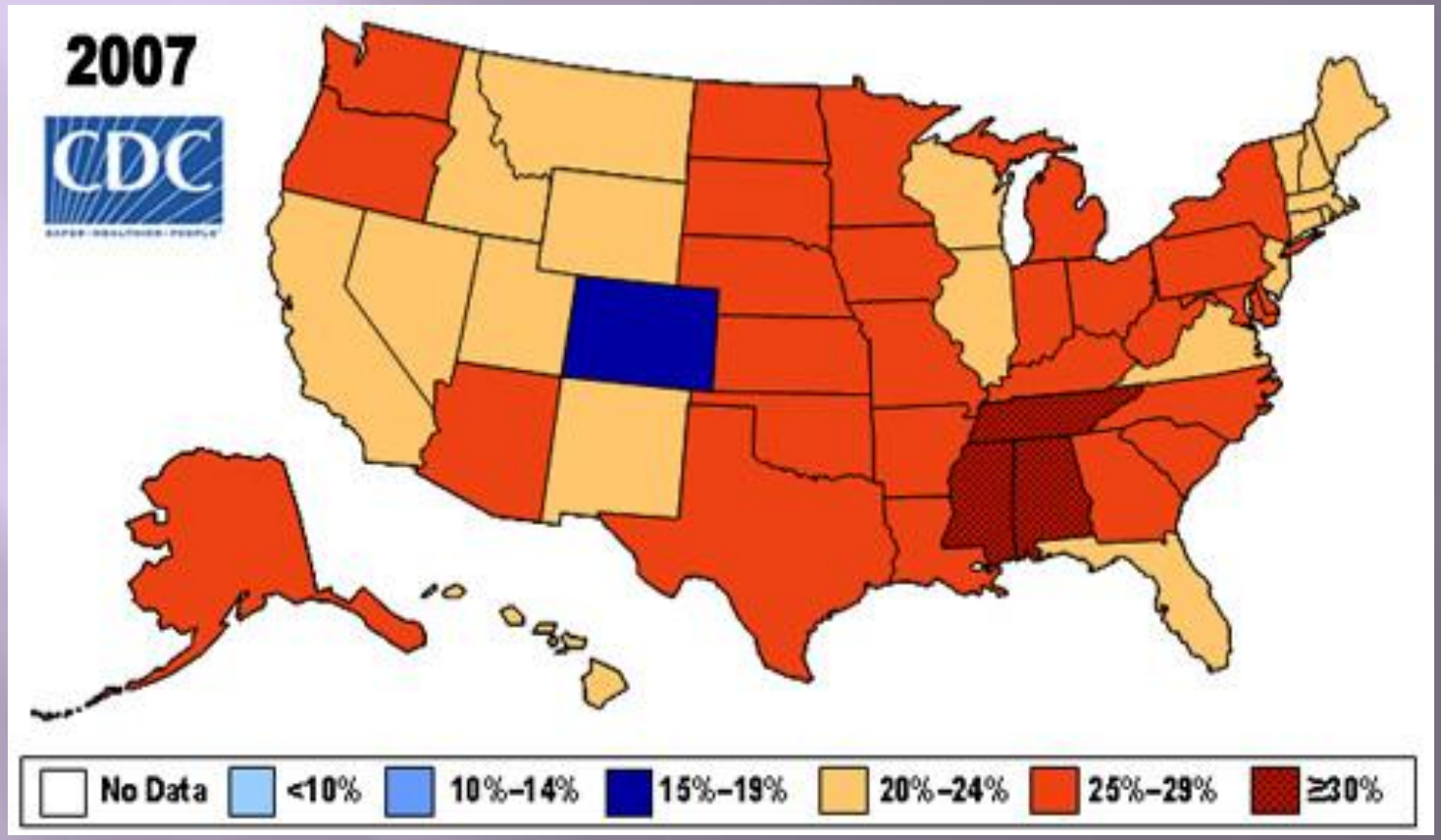
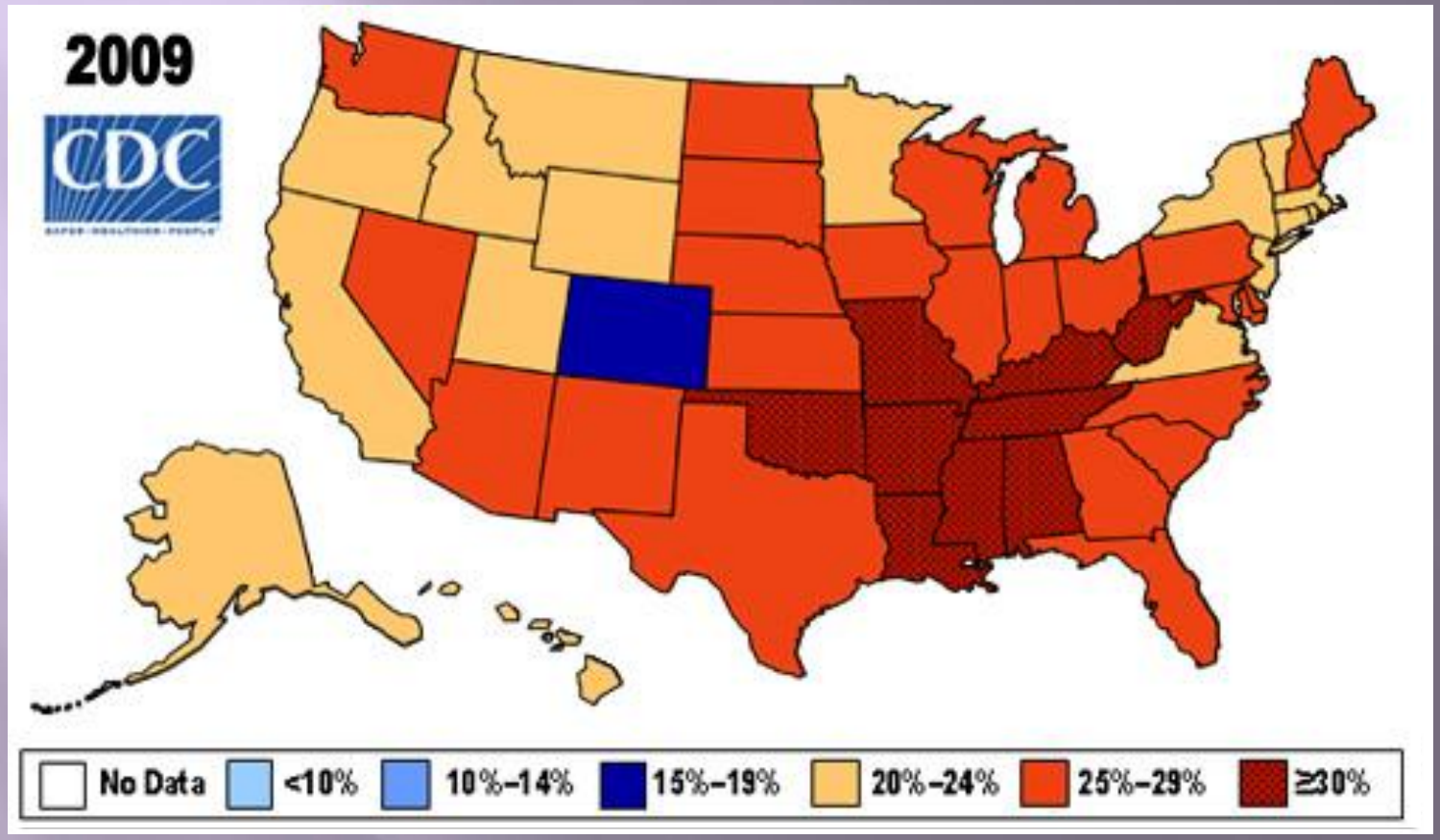


Percent of Obese (BMI ≥ 30) in U.S. Adults



Percent of Obese (BMI ≥ 30) in U.S. Adults



APPLIED RESEARCH DIRECTED TOWARD DEVELOPING HEALTHIER PEOPLE

- Obesity – Nutrition + Lifestyle Interventions

O'Connor TM, Hilmers A, Watson K, Baranowski T, Giardino AP. **Feasibility of an obesity intervention for paediatric primary care targeting parenting and children: Helping HAND.** Child Care Health Dev. 2011 Nov 9. doi: 10.1111/j.1365-2214.2011.01344.x. [Epub ahead of print]

……. *Helping HAND, a 6-month intervention, targeted children with body mass index 85-99%tile and their parents. Intervention group attended monthly sessions and self-selected child behaviours and parenting practices to change.*

Thompson D, Baranowski T, Buday R, Baranowski J, Thompson V, Jago R, Griffith MJ. **Serious Video Games for Health How Behavioral Science Guided the Development of a Serious Video Game.** Simul Gaming. 2010 Aug 1;41(4):587-606.

……. *behavioral science guided the design of a serious video game health messages of how to prevent Type 2 diabetes and obesity among youth. Video game designers and behavioral scientists worked together to create a highly focused serious video game that entertains while promoting behavior change.*

APPLIED RESEARCH DIRECTED TOWARD DEVELOPING HEALTHIER PEOPLE

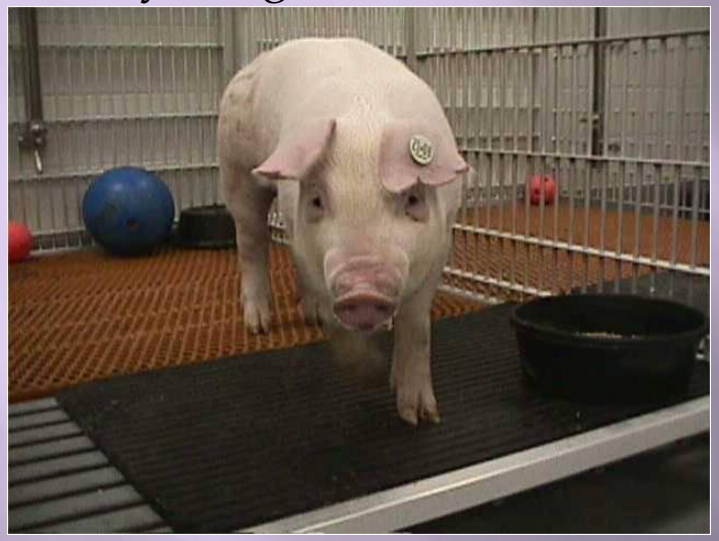
- Obesity – The intersection of many factors beyond genomics and diet

Butte NF, Puyau MR, Vohra FA, Adolph AL, Mehta NR, Zakeri I.
Body size, body composition, and metabolic profile explain higher energy expenditure in overweight children. J Nutr. 2007 Dec;137(12):2660-7.

Numerous factors associated with obesity and energy intake including net mechanical energetic efficiency, sex, Tanner stage, fat free mass, fat mass (FM), fasting serum nonesterified fatty acids , leptin, free thyroxine, triiodothyronine, and 24-h urinary norepinephrine and epinephrine.

APPLIED RESEARCH DIRECTED TOWARD DEVELOPING HEALTHIER PEOPLE

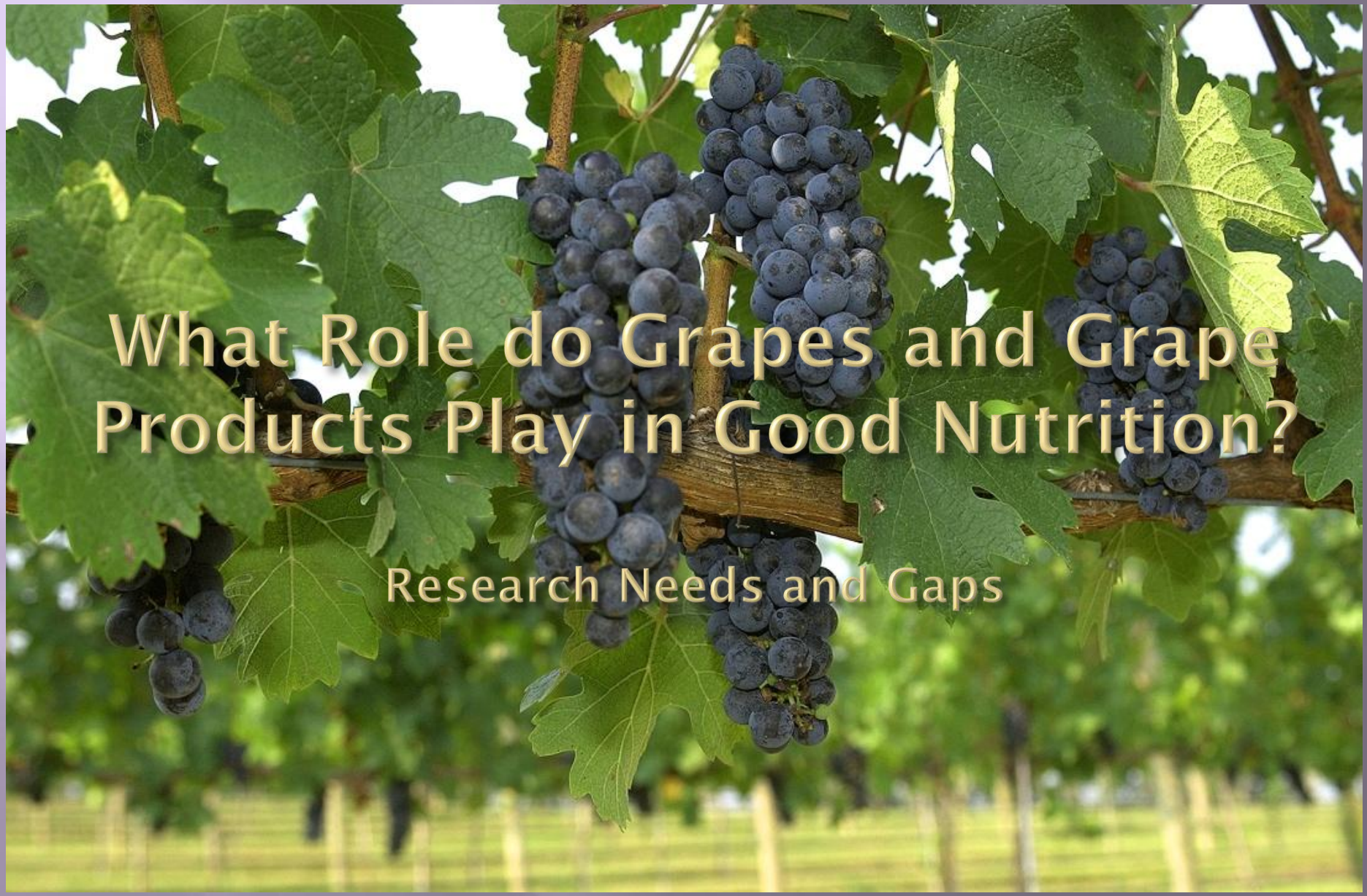
- Obesity – The intersection of many factors beyond genomics and diet



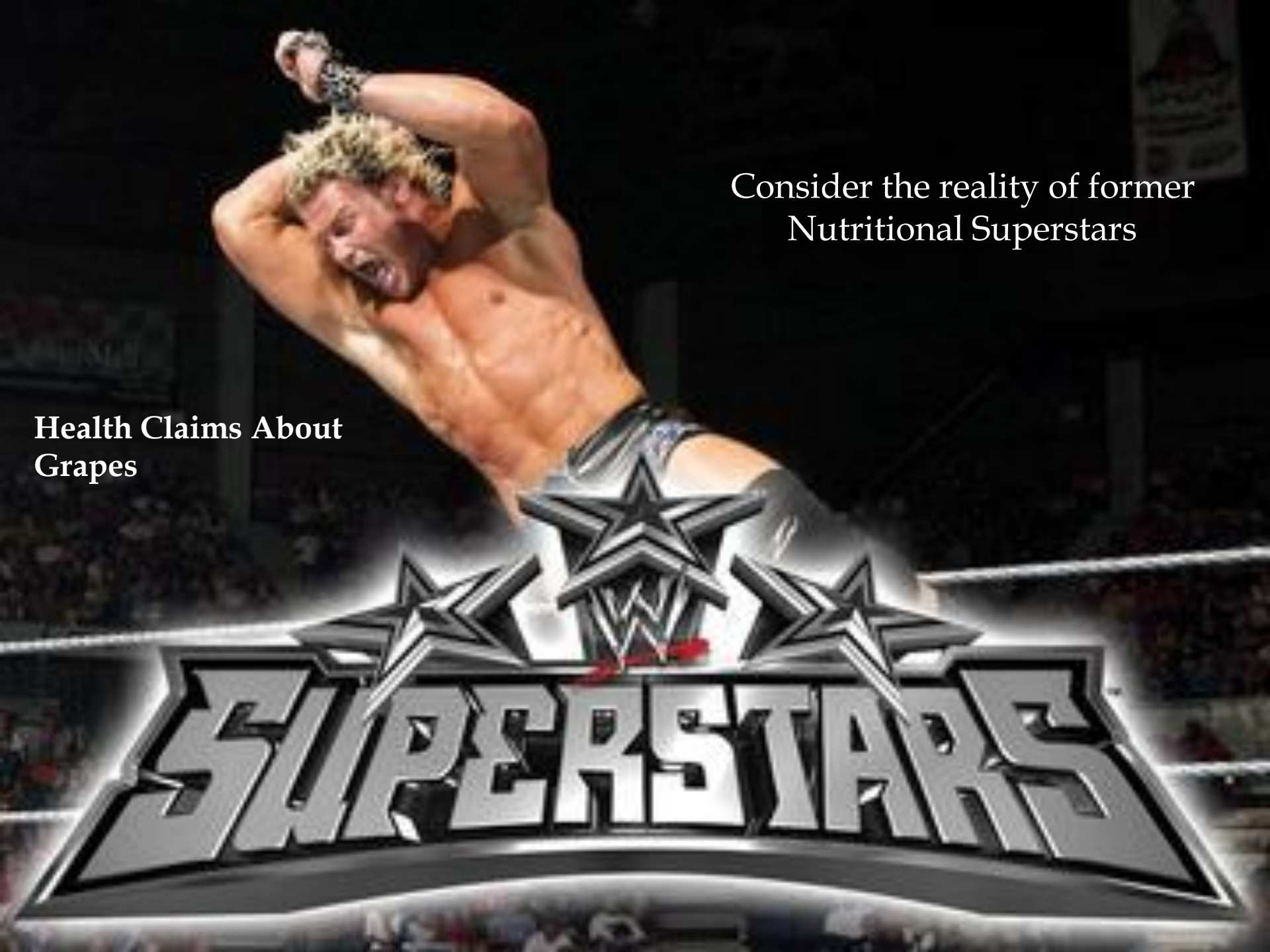
Robert W. Li, Sitao Wu, Weizhong Li, Karl Navarro, and Robin D. Couch, Dolores Hill, **Joseph F. Urban, Jr.** **Alterations in the porcine colon microbiota induced by the gastrointestinal nematode Trichuris suis** Epub ahead of print Infect. Immun. doi:10.1128/IAI.00141-12

Work that shows that the microbiota in the pig's intestinal tract is changed by presence of a parasite, Trichuris suis, and that this resulted in large changes in metabolism

Shankar K, Kang P, Harrell A, Zhong Y, Marecki JC, **Ronis MJ, Badger TM.** Maternal overweight programs insulin and adiponectin signaling in the offspring. *Endocrinology*, 151: 2577-89, 2010.


What Role do Grapes and Grape Products Play in Good Nutrition?
Research Needs and Gaps

- **Health benefits of grapes**
- Grapes are rich in polyphenolic …**resveratrol**. Resveratrol … plays protective function against cancers , coronary heart disease (CHD), degenerative nerve disease, Alzheimer's disease and viral/ fungal infections.
- **Resveratrol** reduces stroke risk
- Anthocyanins are another class of polyphenolic anti-oxidants …. have been found to have anti-allergic, anti-inflammatory, anti-microbial, as well as anti-cancer activities.
- **Catechins**, a type of flavonoid tannin group of anti-oxidants found in white/green varieties has also shown to have these health protecting functions.
- In addition, the berries are very low in calories. 100 g fresh grapes just provide 69 calories but zero cholesterol levels.
- Grapes are rich source of micronutrient minerals like copper, iron and manganese. Copper and manganese are an essential co-factor of antioxidant enzyme, superoxide dismutase. Iron is specially concentrated more in raisins. In addition 100 g of fresh grapes contain about 191 mg of health benefiting electrolyte, **potassium**.
- They are also good source of **vitamin-C**, vitamin A, vitamin K, carotenes, B-complex vitamins such as pyridoxine, riboflavin, and thiamin.



Consider the reality of former Nutritional Superstars

Health Claims About Grapes

SELENIUM SUPERSTAR

Selenium: A trace mineral with ***antioxidant properties***, selenium may be useful in preventing ***arthritis*** and other conditions, including ***age-related blindness, cancers, cardiovascular disease, cataracts and kidney disease***. You'll get selenium from whole-grain **wheat products and shellfish**, such

SELENIUM AND CANCER – THE GREAT NUTRITIONAL STAR

- PUBMED:
  - Selenium & Cancer = > 3,500 hits – most showing positive benefit
  - Selenium & Cancer & Epidemiology ~ 400 hits, most positive benefit
  - Selenium & Cancer & Clinical Trial ~ 600 hits, most positive benefit

THE NUTRITIONAL PREVENTION OF CANCER (NPC) TRIAL

- 1312 participants; mean age = 63
- Intervention – 200 ug Se/d as Se-enriched yeast

  or placebo

- Primary endpoint = skin cancer

RESULTS

- Slight increase in benign skin cancer

- BUT secondary analysis =
  - 50% decrease in all cancer mortality
  - 70% decrease in prostate cancer
  - Significant reduction in lung and colo-rectal cancer

FDA Qualified Health Claim:

"Selenium may reduce the risk of certain cancers. Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive."

THE SELECT TRIAL

- Largest prostate cancer trial ever funded by NIH

- 35,000 participants
- 200 ug Se/d (as selenomethionine) or vitamin E (400 I.U./d as D,L alpha-tocopherol) or placebo
- Planned for 12 years, but stopped at interim:

THE SELECT TRIAL

- Largest prostate cancer trial ever funded by NIH

- 35,000 participants
- 200 ug Se/d (as selenomethionine) or vitamin E (400 I.U./d as D,L alpha-tocopherol) or placebo
- Planned for 12 years, but stopped at interim:
  - **NO benefit to cancer**
  - **Slightly elevated (non-significant)diabetes risk from Se**
  - **SIGNIFICANT INCREASE in prostate cancer from vitamin E**

THE SELECT TRIAL

- Largest prostate cancer trial ever funded by NIH

- 35,000 participants
- 200 ug Se/d (as selenomethionine) or vitamin E (400 I.U./d as D,L alpha-tocopherol) or placebo
- Planned for 12 years, but stopped at interim:
  - NO benefit to cancer
  - Slightly elevated diabetes risk from Se

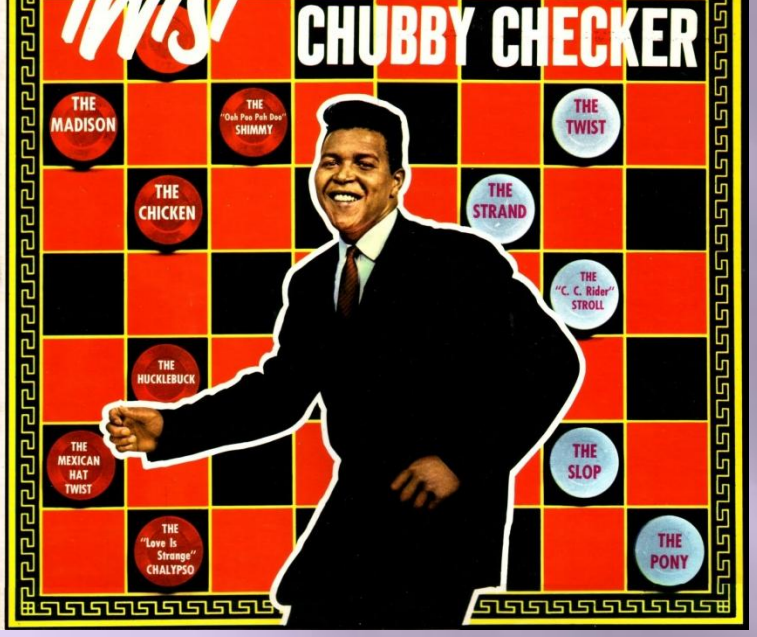
FDA amended Health Claim:

"Two weak studies suggest that selenium intake may reduce the risk of prostate cancer. However, four stronger studies and three weak studies showed no reduction in risk. Based on these studies, FDA concludes that it is highly unlikely that selenium supplements reduce the risk of prostate cancer."

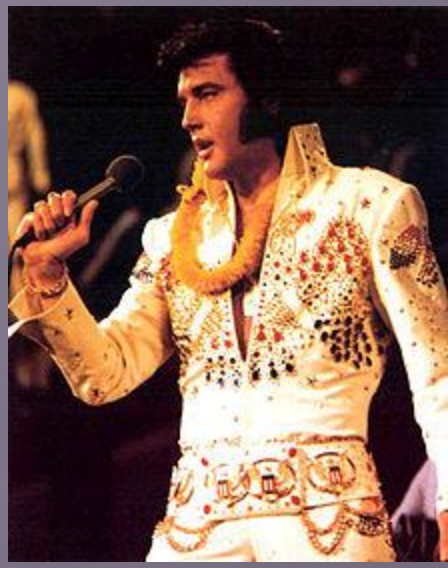
Selenium: Ongoing trials to reverse negative press and boost sagging sales?

According to new data from SPINS, sales of supplements with selenium as the principle ingredient **were $4.7 million for the current** 52-week period ending May 2011 from $5.5 million versus the prior period.

Paul Willis, CEO and president from Cypress Systems, a Fresno-based biotechnology company and producer of high selenium yeast, said that decline is due *"in large part to the **negative press created by the 2008 termination of the SELECT trial** by the National Cancer Institute (NCI)".*



AND SOME SUPERSTARS FROM YESTERDAY



ATBC trial: β-carotene supplementation = 18% INCREASE in lung cancer (29,000 male smokers)

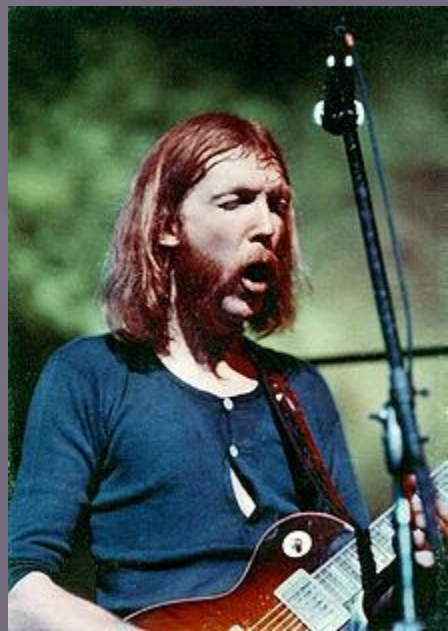
PNAS report of Ristow et al: Antioxidants prevent health-promoting effects of physical exercise in humans

JAMA meta analysis: Treatment with beta carotene, vitamin A, and vitamin E may increase mortality.

AND SOME MORE SUPERSTARS FROM YESTERDAY

Natl Cancer Inst. 2007 Jul 18;99(14):1074-85. Epub 2007 Jul 10. **The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer.** Kavanaugh CJ, Trumbo PR, Ellwood KC.

. The FDA found **no credible evidence** to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial, or pancreatic cancer. The FDA also found **no credible evidence** for an association between tomato consumption and a reduced risk of lung, colorectal, breast, cervical, or endometrial cancer. The FDA found **very limited evidence** to support an association between tomato consumption and reduced risks of prostate, ovarian, gastric, and pancreatic cancers.



AND ITS NOT JUST THE SCIENCE NEWS THAT'S BAD ……..

- **EFSA mass rejects probiotics and antioxidants as article 13.1 batch two published**

By Shane Starling, 25-Feb-2010; Beverage Daily.com

The European Food Safety Authority (EFSA) has issued negative opinions to 'most' of 416 health claim dossiers including submissions linking health benefits to vitamin D, probiotics, green tea, black tea, lutein, beta glucans, meso-zeaxanthin, alpha-lipoic acid and melatonin.

.

AND ITS NOT JUST THE SCIENCE NEWS THAT'S BAD ……..

Nestle Healthcare Nutrition, 12/3/09

Department of Health and Human Services

Public Health Service
Food and Drug Administration College Park. MD 20740 **DEC 03 2009**

David Yates
President
Nestle HealthCare Nutrition

Dear Mr. Yates:

This is to advise you that the Food and Drug Administration (FDA) reviewed your websites at the Internet addresses http://www.Nestle-Nutrition.com, www.NestleNutritionStore.com, and http://www.kidessentials.com in November 2009. Your BOOST Kid Essentials Nutritionally Complete Drink (Vanilla, Chocolate, and Strawberry flavors) is promoted on your websites as a "medical food," and the labeling claims on your websites represent the product as a medical food

SO HOW CAN WE AVOID THESE POTHOLES IN THE ROAD?????

The need for Evidenced-Based nutrition

Evidence-based medicine (EBM)

(from Wikipedia)

- Applies the best available **evidence** gained from the scientific method to medical **decision making**.

- Assesses the quality of evidence of the risks and benefits of treatments (including lack of treatment).

- EBM seeks …..to apply these methods to ensure the best **prediction** of outcomes in medical treatment.

SCIENTIFIC EVIDENCE FOR THE FUNCTION OF A FOOD INGREDIENT:

1. Predicted (no evidence); Organic food is more nutritious ?


DAILY EXPRESS

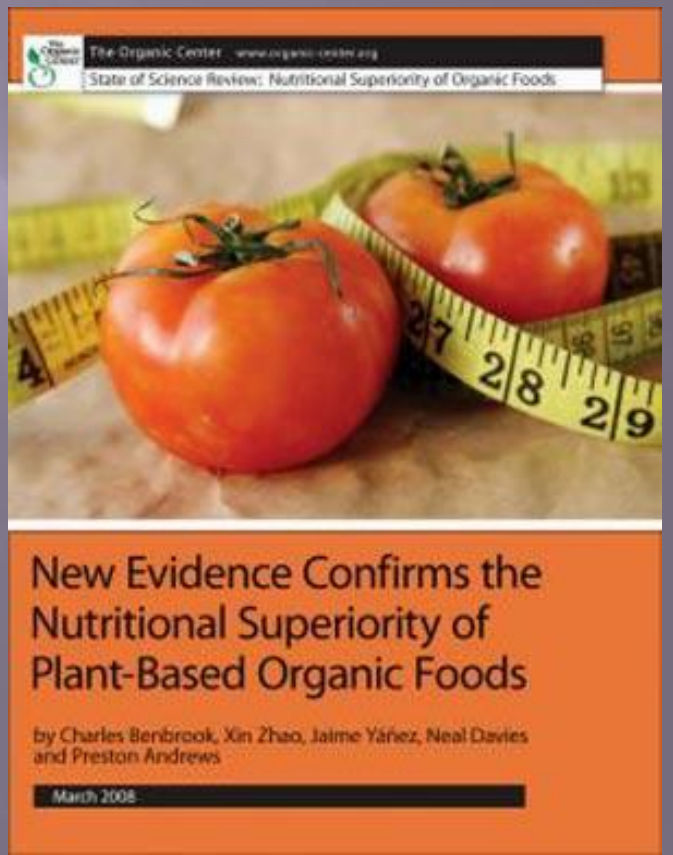
New wonder cream that gives women a big lift

£5 OFF YOUR SHOPPING BILL AT Lidl

ORGANIC FOOD NO HEALTHIER

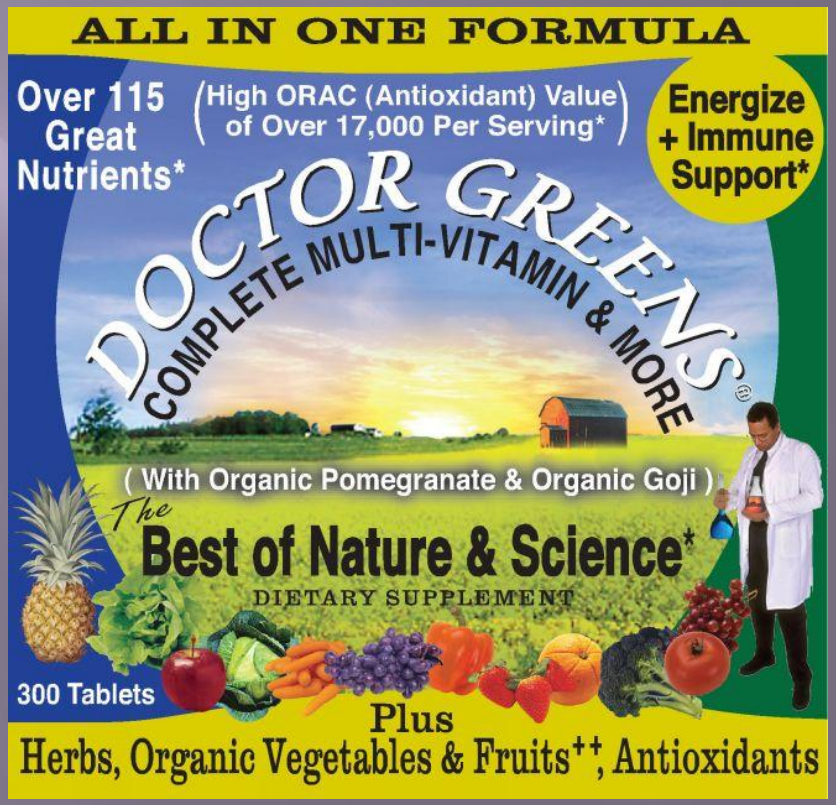
OFFICIAL

Why did weather men get it all so wrong about summer?



SCIENTIFIC EVIDENCE FOR THE FUNCTION OF A FOOD INGREDIENT:

1. Predicted (no evidence); Organic food is more nutritious ?
2. Chemistry; e.g. ORAC



SCIENTIFIC EVIDENCE FOR THE FUNCTION OF A FOOD INGREDIENT:

1. Predicted (no evidence); Organic food is more nutritious ?
2. Chemistry; e.g. ORAC
3. In vitro; e.g. cell culture

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2. Chemistry; e.g. O
3. In vitro; e.g. cell c
4. Animal studies

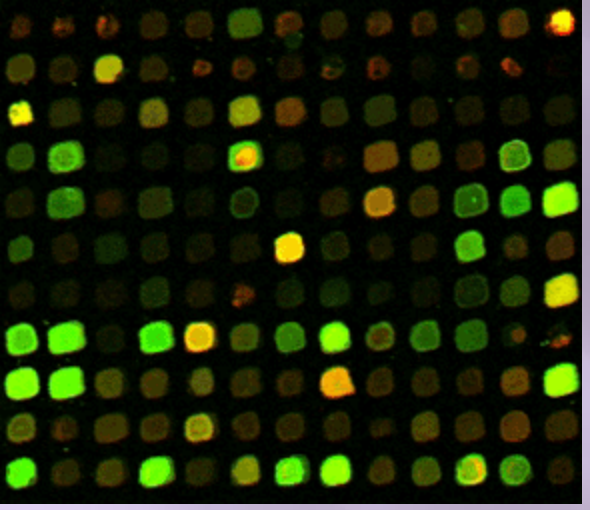
SCIENTIFIC EVIDENCE FOR THE FUNCTION OF A FOOD INGREDIENT:

1. Predicted (no evidence); Organic food is more nutritious ?
2. Chemistry; e.g. ORAC
3. In vitro; e.g. cell culture
4. Animal studies

But all the above only generate

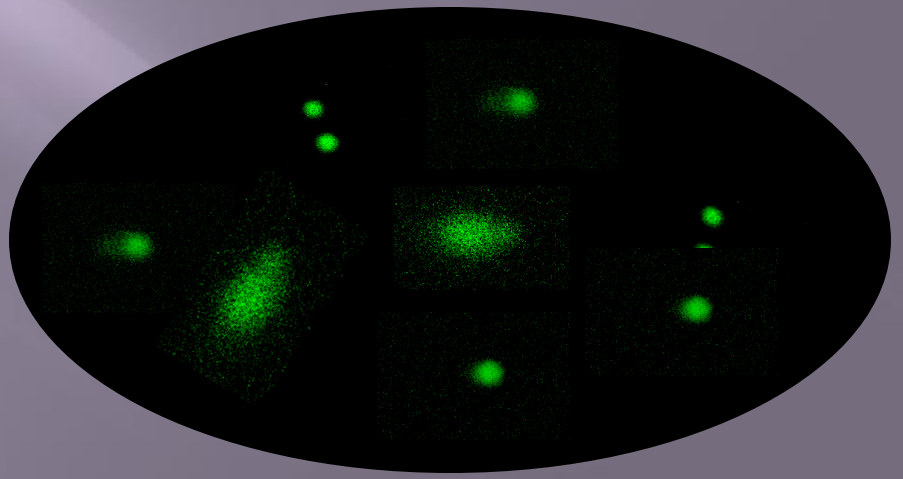
HYPOTHESES

Evidence requires human studies



Epidemiologic evidence
Judging study value:

- Valid biomarkers
  - Many common biomarkers NOT acceptable to FDA
    - *Cancer*
      - *PSA*
      - *COMET assay and similar*
      - *Gene activation*
      - *Enzyme activity*
      - *Circulating cytokines*



Epidemiologic evidence

Judging study value:

- Valid biomarker
- Accurate estimate of intake
  - Validated Food Frequency Questionnaire
    - Secondary measures help validate:
      - Urinary nitrogen ~ protein intake
      - Doubly labeled water ~ energy intake
  - Surrogate markers of intake
    - Serum conc., enzyme activity, etc.

The American Journal of CLINICAL NUTRITION

Validation of a self-administered food-frequency questionnaire administered in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: comparison of energy, protein, and macronutrient intakes estimated with the doubly labeled water, urinary nitrogen, and repeated 24-h dietary recall methods

Anja Kroke, Kerstin Klipstein-Grobusch, Susanne Voss, Jutta Möseneder, Frank Thielecke, Rudolf Noack and Heiner Boeing ; AJCN1999, 70, 439-447

Epidemiologic evidence

Judging study value:

- Valid biomarker
- Accurate estimate of intake

- Relevant/Adequate survey population
- Valid baseline or comparative group
  - DRUGS cure ill health, *FOOD maintains good health*
  - Use Healthy subjects

Epidemiologic evidence
Judging study value:

- Valid biomarker
- Accurate estimate of intake
- Relevant/Adequate survey population
- Valid baseline or comparative group

- Lack of 'bias'

Bias	Most often encountered	Solution
Selection	Case/control/RPC	Care in selection/none
Recall	Retrospective	Care/statistics
Attrition	Prospective/RPC	None/statistics
Detection	All	Validate all measures
Expectation	All	Objective measures
Compliance	RPC	Control measures
Confounding	All/esp. Epideme	Statistics

USDA ars

Epidemiologic evidence
Judging study value:

- Valid biomarker
- Accurate estimate of intake
- Relevant/Adequate survey population
- Valid baseline or comparative group
- Lack of 'bias'
- Adequate statistics
  - Sample size (Power analysis)
  - Randomization
  - Sequence effects (e.g. day length)
  - Proper design
    - Controls
    - Validated measures

Epidemiologic evidence
Judging study value:

- Valid biomarker
- Accurate estimate of intake
- Relevant/Adequate survey population
- Valid baseline or comparative group
- Lack of 'bias'
- Adequate statistics
- Are conclusions justified?
  - Do data support conclusions?
  - Where are conclusions published?
  - Are they relevant to the target population?
  - Do they fit known chemistry/metabolism?

Intervention studies – Food, NOT drugs

Intervention Studies

1. Conceptualization/need
   - Purpose of study
   - Background/history


Supplement Facts

Exploratory research?

Data for label/claims/advertising?

Toxicity?

GRAS?

FDA U.S. Food and Drug Administration CENTER FOR FOOD SAFETY AND APPLIED NUTRITION Department of Health and Human Services

Federal Trade Commission Protecting America's Consumers

Intervention Studies

1. Conceptualization/need
2. Design - Statistical
   - Involve a statistician at BEGINNING!
   - Make only valid/necessary measures
     - Remember "p=0.05" means chance alone accounts for 5/100 sig. differences
     - Make contrasts *a priori*
     - Avoid 'data mining'
   - Design
     - Repeated measures?
       - Adequate washout?
     - Simple randomized block?
     - Have you adjusted for: gender, age, menopause, smoking, general health, screening clinicals, day length, physical activity, baseline diet, supplement use?

Intervention Studies

1. Conceptualization/need
2. Design – Statistical
3. Use the correct population

What is the objective?

Top questions for Grape/Wine

1. What do you want to do?
   a. Sell more product
      a. Which products?
      b. Are you willing to treat products differently (e.g. raisins vs table grapes vs grape seed extract vs wine)?
   b. Ascertain health benefits
2. What is the state of the nutritional data?
   a. A critical analysis
   b. How would FDA/IOM view the evidence?
   c. How universal are results?
   d. What are the gaps (see question 1)?
3. How much do you have to spend (a discount clinical trial may not be worth the money)
4. Who should be approached for collaboration?